Assessment of Optic Nerve Head Parameters using Optical Coherence Tomography Angiography in Behçet Uveitis Patients with Healthy Controls

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ABSTRACT

Purpose: To compare the optical coherence tomography angiography (OCTA) findings of Behçet uveitis (BU) patients with healthy controls and to evaluate their correlation with the best corrected visual acuity (BCVA).

Methods: We conducted a thorough ophthalmic examination and OCTA on 20 BU patients and 26 control subjects. Optic nerve head (ONH) flow and non-flow areas, capillary vessel density (CVD) at the optic disc, superficial capillary plexus (SCP) flow and non-flow areas (FAZ), outer retina and choriocapillaris (CC) flow areas, and SCP thickness at the parafoveal region were measured using OCTA.

Results: We found significantly lower ONH flow area (1.57±0.17 vs. 1.68±0.08 mm^2) and CVD at the optic disc (OD)-centered 4.5x4.5 mm^2 area (53.99±4.94 vs. 58.13±1.77%) ($p<0.05$) but higher ONH non-flow area (0.44±0.23 vs. 0.27±0.10 mm^2, p=0.040) in BU patients compared to the controls. There was no significant difference in SCP flow and non-flow areas (FAZ), outer retina and CC flow areas and parafoveal SCP thickness between the two groups (p>0.05). There was a negative correlation between BCVA (logMAR) and the ONH flow area (r= -0.363, p=0.049), SCP flow area (r= -0.703, p<0.001), parafoveal SCP thickness (r= -0.348, p=0.035) and CVD in the OD-centered area (r= -0.644, p=0.002) in BU patients.

Conclusion: While there were no micro-vascular changes at the parafoveal region. The CC, ONH-related parameters such as decreased ONH flow area and CVD at the optic disc and increased ONH non-flow area were observed regardless of disease duration and visual acuity in BU patients.

Keywords: Behçet uveitis, Optic nerve head, Optical coherence tomography angiography.

INTRODUCTION

Behçet disease (BD) is a multi-systemic vasculitis involving vessels of all sizes. The characteristic feature of ocular inflammation is recurrent vaso-occlusive vasculitis of an explosive nature. Due to the vascular involvement of Behçet disease, fluorescein angiography (FA) is accepted as the gold standard tool for evaluation of vascular occlusions, peripheral retinal ischemic areas, neovascularization and vascular leakage by demonstrating the activity of the disease.[1] However, FA is a relatively invasive process which might cause allergic reactions ranging from nausea to anaphylaxis. Additionally, the late phase of FA is not appropriate to show non-flow areas (FAZ) or nonperfusion areas due to leakage of the dye from the abnormal vessels.[2]

Primary choroidal vessel involvement as choroidal vasculitis and secondary choroidal inflammation as a result of severe retinal inflammation have also been reported.[3] Diffuse and focal infiltrations of the choroid with lymphocytes and macrophages have been revealed as histopathological findings.[4,5] Indocyanine green

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**Running Head: Optic Nerve Head using OCT-A in Behçet Uveitis*

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angiography (ICGA) signs of choroidal involvement in BD including hypo- and hyper-fluorescent spots, irregular filling of the choriocapillaris, choroidal filling defects, staining of and leakage from choroidal vessels, and optic disk and diffuse choroidal hyperfluorescence in the intermediate or late phase of ICGA have been described.[6-8]

OCTA has been developed for non-invasive imaging of the retinal and choroidal microvasculature without the need for a dye injection and has allowed the study of the retinal vascular plexuses, especially demonstrating the retinal vascular structure layer by layer, and showing the superficial capillary plexus (SCP), deep capillary plexus (DCP) and choriocapillaris (CC) flow area in separate manner.[9,10]

The recent report by Khairallah et al. demonstrated that OCTA visualized and characterized perifoveal micro-vascular changes better than FA in eyes with active Behçet uveitis.[11] To best of our knowledge, there is no study in the literature comparing the optic nerve head (ONH) flow and non-flow area and the capillary vessel density (CVD) at the center of the optic disc in Behçet patients.

The aim of this study was to compare micro-vascular changes of the parafoveal retina and ONH in Behçet patients and healthy subjects using OCTA and to correlate our results with the best-corrected visual acuity (BCVA).

MATERIALS AND METHODS

This retrospective study was conducted at the Uveitis and Behçet Unit of the Eye Department of Izmir Katip Celebi University Ataturk Education and Research Hospital. The study was approved by the Institutional Ethics Committee of Izmir Katip Celebi University, School of Medicine (21 November 2016, No. 279). The study was conducted in accordance to the tenets of the Declaration of Helsinki.

The study group consisted of subjects diagnosed with Behçet Uveitis (BU). Behçet Uveitis defines those patients with posterior segment involvement in ocular Behçet's disease which met the 1990 classification criteria of the International Study Group for Behçet's Disease.[12]

All patients in the study group were in stable clinical remission. The exclusion criteria were the presence of significant media opacities such as dense cataract, vitreous haze or vitreous hemorrhage; poor fixation that did not allow obtaining images of adequate quality; intraocular pressure > 21 mmHg; a refractive error greater than 3 diopters; and the diagnosis of any other confounding ocular pathology such as diabetic retinopathy, hypertension, glaucoma, or optic neuropathy.

All participants had undergone a complete ophthalmologic examination including BCVA and intraocular pressure measurement, fundus examination, spectral-domain OCT, and OCTA. Additionally, FA was performed in patients with BU.

Optical Coherence Tomography Angiography

We used the Optovue RTVue XR 100 Avanti (Optovue Inc., Fremont, CA, USA, version: 2016.1.0.12) with the split spectrum amplitude decorrelation algorithm (SSADA) to obtain OCTA images for all subjects who met the diagnostic criteria. Motion artifacts were reduced with the motion correction technology (MCT) software. The device uses a wavelength of 840 nm and a bandwidth 50 nm and can obtain 70,000 A-scans per second. The OCTA images obtained were 6 x 6-mm in size from the macula and 4.5 x 4.5-mm from the optic nerve head. Two orthogonal OCTA volumes were acquired to perform motion correction. The scans were repeated if image quality was unsatisfactory. *En face* OCT images were compared with the corresponding *en face* structural images and cross-sectional OCTA to detect the presence of signal loss and shadowing. Only scans without significant motion artifacts and with a signal strength index > 60 were taken into account.

Vascular layers segmentation and flow density analysis

Vascular retinal layers were visualized and segmented as previously described.[13,14] Two masked investigators (MBY and ND) independently checked the segmentation quality before image analysis. The software has in-built segmentation (superficial and deep retinal vascular plexi (SCP and DCP), outer retina and choriocapillaris (CC)) but manual segmentation was used to confirm the findings on OCTA. Flow, non-flow and density measurements were also performed on the optic disc. Density measurements were performed both inside the disc and at the peripapillary area with the standard measurement technique of the device.

Statistical analysis

The IBM SPSS Statistics (23.0) package software was used for the analyses. The chi-square test was used to compare categorical variables between the two groups. The Shapiro-Wilk test was used to determine the conformance of the numerical variables with a normal distribution in the two groups. We employed the Independent samples t test to compare the numerical variables that had a normal distribution and the Mann-Whitney Test to compare the others between the groups. The linear relationship between numerical variables was evaluated with Spearman rho correlation analysis. A p value <0.05 was considered statistically significant.

RESULTS

Demographic characteristics

The age and gender characteristics of the Behçet uveitis group and the healthy controls were similar ($p > 0.05$). The mean age of the 8 (40%) female and 12 (60%) male Behçet patients was 42.70 ± 12.02 (25-72 years) years and the mean follow-up duration was 68.15 ± 32.14 (19-114 months) months. The control group included 26 healthy participants consisting of 16 (61.5%) females and 10 (38.4%) males with a mean age of 44.46 ± 14.46 (16-76 years) years. There was no statistically significant difference in age or gender between the BU patients and healthy controls ($p > 0.05$) (Table 1). The most common complication of ocular Behçet was epimacular membrane (in 8 eyes (20%)) (Table 1). Cataract surgery and vitreoretinal surgery had previously been performed in 1 and 2 eyes, respectively.

Optical coherence tomography angiography analysis

The OCTA data of both eyes of the subjects are listed in Table 2. The Behçet patients had significantly decreased capillary vessel density (CVD) at the optic disk (OD)-centered 4.5 x 4.5 mm^2 area (53.99 ± 4.94 vs. 58.13 ± 1.77, p = 0.030), lower ONH flow area (1.57 ± 0.17 vs. 1.68 ±

Table 1. *Demographic and clinical features of the groups.*

	Behçet's disease (*n* = 20)	Healthy controls (*n* = 26)	*P*- value
Age (years), mean ± SD	42.70 ± 12.02	44.46 ± 14.46	0.662[a]
Gender (female / male), n (%)	8 (40) / 12 (60)	16 (61.5) / 10 (38.5)	0.147[b]
Follow-up duration (months), mean ± SD	68.15 ± 32.14	-	
Epimacular membrane, n (%)*	8 (20)	-	
Macular scar, n (%)*	5 (12.5)	-	
Optic disc pallor, n (%)*	5 (12.5)	-	
Retina pigment epithelium change, n (%)*	5 (12.5)	-	
Intraretinal cystoid change, n (%)*	1 (2.5)	-	
Fibroglial tissue proliferation from the optic nerve head, n (%)*	1 (2.5)	-	

[a]; t-test [b]; Pearson Chi-Square test
* The numbers given are the number of eyes. Percentages were calculated over 40 Behçet uveitis eyes.

Table 2. *Optic coherence tomography angiography measurements in Behçet uveitis patients (n = 20) and healthy control subjects (n = 26).*

Variable	Right Eye			Left Eye		
	Behçet disease	Control	*P*- value[a]	Behçet disease	Control	*P*- value[a]
Visual acuity at the time of measurement (logMAR), Median, (min-max)	0.10 (0-3.00)			0.18 (0-3.00)		
Superficial capillary plexus flow area, mm^2	1.24 ± 0.27	1.36 ± 0.16	0.115	1.22 ± 0.29	1.35 ± 0.16	0.123
Superficial capillary plexus nonflow area (FAZ), mm^2	0.34 ± 0.16	0. 36 ± 0.12	0.650	0.474 ± 0.472	0.35 ± 0.14	0.412
Outer retina flow area, mm^2	1.21 ± 0.17	1.23 ± 0.19	0.509	1.14 ± 0.15	1.23 ± 0.25	0.095
Choriocapillaris flow area, mm^2	1.89 ± 0.11	1.90 ± 0.07	0.822	1.85 ± 0.20	1.91 ± 0.07	0.557
Optic nerve head flow area, mm^2	1.57 ± 0.17	1.68 ± 0.08	0.033	1.38 ± 0.19	1.64 ± 0.13	0.003
Nerve head nonflow area, mm^2	0.44 ± 0.23	0.27 ± 0.10	0.040	0.37 ± 0.31	0.29 ± 0.17	0.885
Capillary vessel density in disc-centered 4.5 x 4.5 mm area, %	53.99 ± 4.94	58.13 ± 1.77	0.030	52.80 ± 3.46	57.01 ± 3.06	0.007
Parafoveal superficial capillary plexus thickness, µm	122.50 ± 14.62	124.78 ± 9.29	0.885	120.00 ± 20.93	120.17 ± 23.07	0.704

[a]; Mann-Whitney U Test

0.08 mm^{2,} p=0.033) and higher ONH non-flow area (0.44 ± 0.23 vs. 0.27 ± 0.10 mm^2, p = 0.040) in the right eye compared to the control group. There was no significant difference in SCP flow and non-flow areas, outer retina and CC flow area and parafoveal SCP thickness between the two groups (p > 0.05). Besides, there was no significant correlation between disease duration and other OCTA data including the ONH flow area, ONH non-flow area, CVD in disc-centered 4.5 x 4.5 mm^2 area, SCP flow area, SCP non-flow area, outer retina and CC flow areas in both eyes of Behçet patients (p > 0.05).

Correlation of best corrected visual acuity with optical coherence tomography angiography parameters

Evaluation of the right and left eyes (n = 40) of BU patients (n = 20) revealed a negative correlation between the BCVA (logMAR) and ONH flow area (r = -0.363, p = 0.049), SCP flow area (r = -0.703, p < 0.001), CVD in disc-centered 4.5 x 4.5 mm^2 area (r = -0.644, p = 0.002) and parafoveal SCP thickness (r= -0.348, p = 0.035) (Table 3).

Table 3. Correlation of visual acuity (logMAR) with optical coherence tomography angiography parameters in patients with Behçet uveitis (right and left eyes, n = 40)

	Correlation coefficient	***P*- value**
Optic nerve head flow area	-0.363	0.049
Optic nerve head nonflow area	-0.066	0.749
Superficial capillary plexus flow area	-0.703	< 0.001
Superficial capillary plexus nonflow area	0.125	0.475
Outer retina flow area	0.242	0.160
Choriocapillaris flow area	-0.321	0.057
Capillary vessel density in disc-centered 4.5x4.5 mm^2 area	-0.644	0.002
Parafoveal superficial capillary plexus thickness	-0.348	0.035

DISCUSSION

The underlying pathology of Behçet disease is perivascular inflammatory infiltration of the veins, capillaries, and arteries of all sizes, together with a thrombotic vasculopathy.[15] The destructive and recurrent attacks are responsible for irreversible ocular structural changes and indicate a poor prognosis. Recurrent attacks, especially when the posterior segment is involved, increase the risk of potential damage to the sensory retina and uvea and can cause irreversible loss of vision.[16] Macular atrophy, macular inflammatory infiltrate, retinitis, optic disc atrophy and branch retinal vein occlusion have been associated with the visual loss (especially when severe) in BU.[17]

Various imaging modalities are used to visualize diagnostic features, assess disease activity, monitor response to treatment, and detect structural changes in BU patients. Fluorescein angiography (FA) is the gold standard to show the leaky and occlusive nature of retinal vasculitis, capillary non-perfusion areas, macular edema, collateral formation, and neovascularization in these patients.[18,19] Indocyanine green angiography (ICGA) is used to evaluate choroidal involvement.[16] However, a major limitation of both FA and ICGA is the need for dye injection with the potential risk of serious side effects in addition to the fact that they are time consuming. A blurred appearance due to leakage of the dye and/or staining and the variances in the dye transit time also make it difficult to obtain objective measurements.

Optical coherence tomography (OCT) is a standard ancillary test. It enables noninvasive imaging of the vitreomacular interface and the retinal and choroidal structures; measuring the choroidal thickness using the EDI mode of spectral-domain OCT; and detecting non-glaucomatous localized retinal nerve fiber layer (RNFL) defects in BU patients.[20-21] OCT is also very useful for the identification of various patterns of macular edema.[22] On the other hand, FA is superior to OCT for monitoring perifoveal or diffuse retinal capillary leakage and macular or peripheral retinal non-perfusion in BU. Another imaging technique, the ultra-wide-field (UWF) imaging system (OptosPLC, Scotland, United Kingdom), can show a 200° ocular fundus view and has been reported to provide additional information that could alter the management of Behçet patients.[23] Fundus autofluorescence imaging, B-scan sonography, and ultrasound biomicroscopy have also been reported to describe some characteristics of BU.[24, 25]

Optical coherence tomography angiography (OCTA) is a new diagnostic tool that shows reproducible depth-resolved images of the circulation in the retina and choroid without need for a dye injection.[9] It uses the dynamic motion of blood cells to create intrinsic imaging contrast and computes a high resolution 3-dimensional image of the perfused vasculature. OCTA provides segmental assessment of the retinal capillary networks[26] in addition to quantification of ocular pathologies[27] and the microcirculation in the ONH[28] and the peripapillary region.[29] OCTA has been reported to demonstrate retinal ischemia as well as changes in intracapillary spaces in a number of diseases.[30-33]

Khairallah et al.[11] evaluated OCTA findings in 25 patients with active BU and compared with the FA findings. They showed that DCP was more significantly affected than

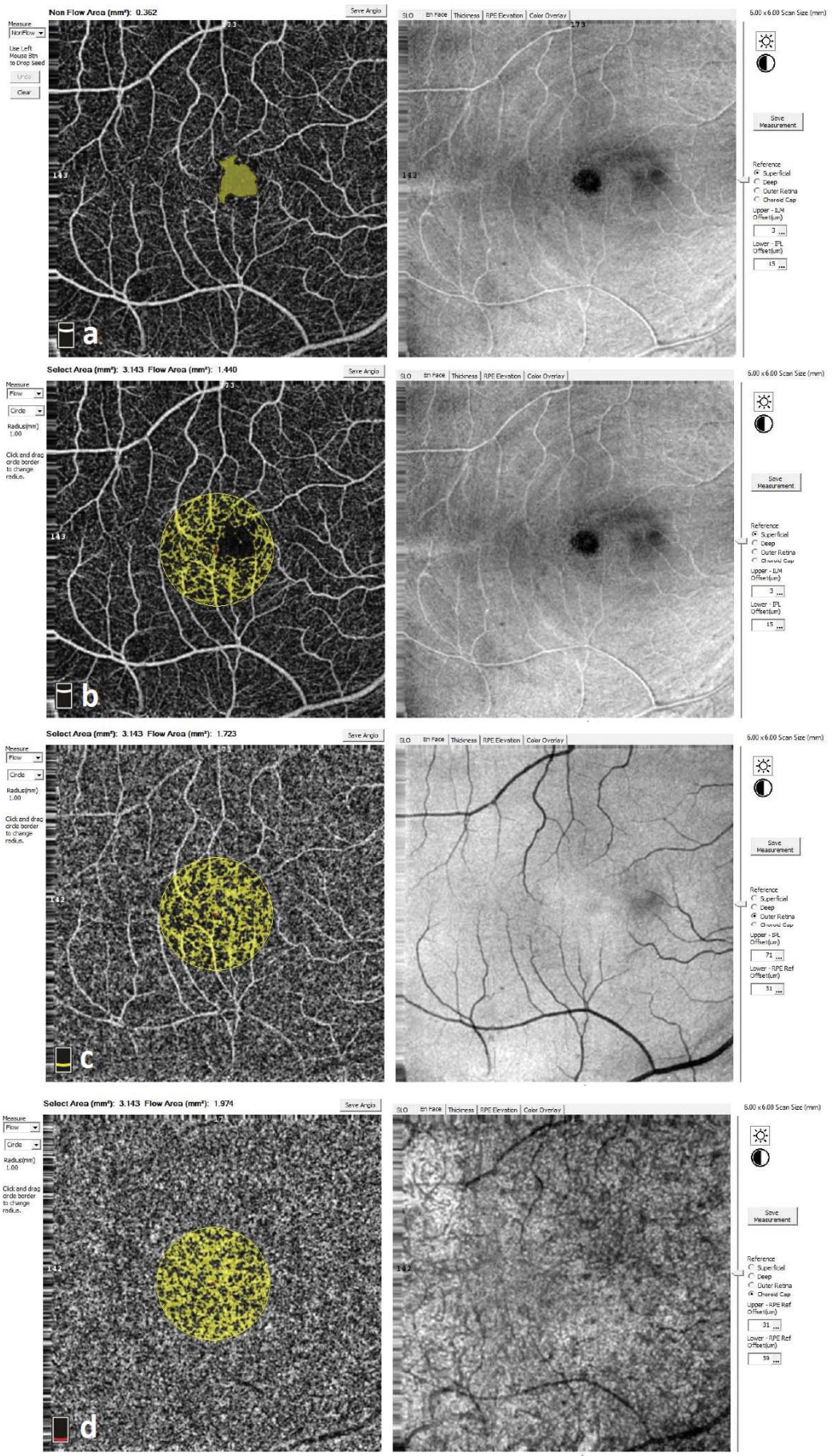

Figure 1. *Optical coherence tomography angiography images of a patient with Behçet uveitis at the 6 x 6-mm macular area.* ***(a),*** *Foveal avascular zone area (0.362 mm²) in the superficial capillary plexus;* ***(b),*** *Flow area (1.440 mm²) in the superficial capillary plexus;* ***(c),*** *Flow area (1.723 mm²) in the outer retina;* ***(d),*** *Flow area (1.974 mm²) in the choriocapillaris.*

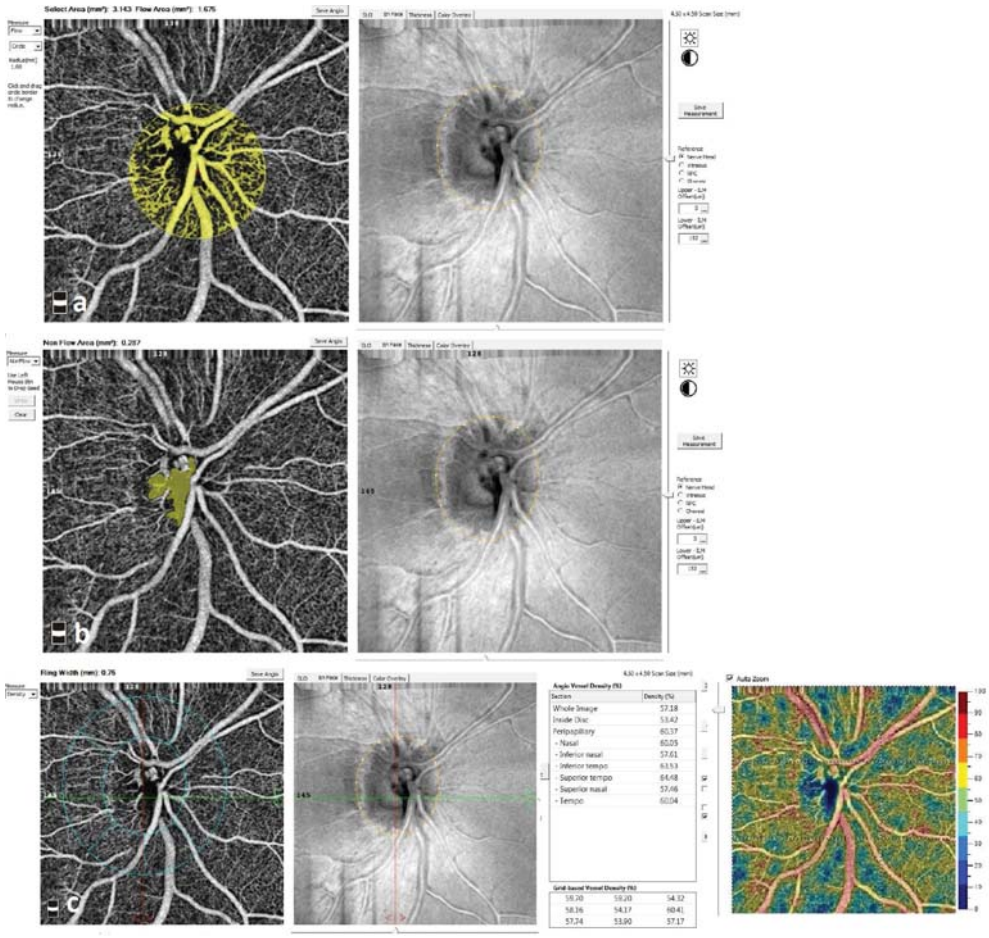

Figure 2. *Optical coherence tomography angiography images of a patient with Behçet uveitis at the optic disc (OD)-centered 4.5 x 4.5 mm² area.* ***(a),*** *Flow area (1.675 mm²) in the OD-centered area;* ***(b),*** *Non-flow area (0.287 mm²) in the OD-centered area;* ***(c),*** *Capillary vessel density (57.18%) in the OD-centered area.*

SCP. They also suggested that OCTA is more capable than FA for a comprehensive evaluation of micro-vascular changes. They found that OCTA showed perifoveal micro-vascular changes (95.5% vs. 59.1%), perifoveal capillary arcade disruption (40.9% vs. 25%), retinal capillary non- and hypo-perfusion areas (86.4% vs. 34.1%) and perifoveal capillary abnormalities (rarefied, dilated and shunting vessels) (84.1% vs. 36.4%) more frequently than FA. The non-perfusion area in DCP was shown to be more severely involved than in SCP, similar to the findings of Somkijrungroj et al.[2] There was no significant difference between the Behçet uveitis patients and healthy groups regarding SCP flow and non-flow areas in our study. Unfortunately, we were unable to assess DCP measurements. On the other hand, Khairallah et al.[11] reported that the FAZ in SCP (0.4 vs. 0.34 mm²) and in DCP plexi (0.72 vs. 0.53 mm²) was comparable between BU patients and the control group. Similarly, there was no difference between the FAZ areas in SCP in the eyes of BU patients and healthy controls in our study (0.34 vs. 0.36 mm² for the right eyes and 0.47 and 0.35 mm² for the left eyes, respectively).

Similar to the study by Khairallah et al.,[11] another study on 16 patients with inactive Behçet uveitis by Emre et al.[34] found more prominent disruption of the retinal micro-vascular structure in DCP than in SCP. Additionally, both superficial CVD and deep CVD results were lower in Behçet cases than healthy subjects. The authors explained that the DCP also seems to be more vulnerable to ischemic processes than SCP as it is not directly connected to arterioles.[2,34] Loss of DCP in OCTA tends to be in the earlier stage of the disease than for SCP. In another study comparing OCTA findings in 15 active and 8 inactive BU patients by Accorinti et al., SCP changes were indicated to be more closely related to active disease.[35] Our results are supported by these studies when the SCP parameter is considered.

A few studies have evaluated ocular parameters in non-ocular BD patients. Comez et al. demonstrated micro-vascular changes in the retinal vascular plexus and CC using OCTA in cases with non-ocular BD.[36] They showed a reduction in the mean SCP, DCP, and CC flow area of the non-ocular BD patients compared to the healthy subjects.

However, no significant difference was observed between the two groups regarding the superficial and deep FAZ area, and the disruption of the normal structure of the capillary network was also not significantly different.[36] Another study has found a significantly lower mean vascular density only involving the SCP in non-ocular BD cases (20 eyes (10 patients)) compared to the control group (20 control eyes) (50.9 % vs. 57.2%).[37] They detected disruption of the perifoveal arcade, vessel rarefaction or perifoveal capillary dilatation with or without telangiectasia in both the SCP and DCP, with predominant involvement of the latter. However, no significant difference was found between the two groups regarding FAZ area measurements in the SCP.[37] These studies have demonstrated that early micro-vascular changes can be considered to have developed in the retinal vascular plexi in patients with non-ocular BD even if no ocular involvement finding is seen with OCTA, as BD is a multi-systemic and chronic recurrent inflammatory disorder. We evaluated the right and left eyes separately and included only ocular Behçet patients in clinical remission in the study group. The SCP flow and non-flow areas, outer retina and CC flow area and parafoveal SCP thickness were comparable in BU patients and the healthy controls.

The study on non-ocular Behçet disease by Goker et al. evaluated the CC flow area at three different points (1 mm, 2 mm, and 3 mm radius areas) and found that the flow area of the CC layer at these three circular zones in the BD group was similar to the healthy group.[38] Another study in non-ocular Behçet patients by Comez et al. has reported a lower CC value in these patients than healthy controls.[36] Kim et al.[39] found that the subfoveal choroidal thickness was significantly higher in both the active and remission phases of BD uveitis compared to the healthy subjects by using enhanced depth imaging optical coherence tomography.[37] These studies indicate increased choroidal thickness together with fluid accumulation due to subclinical choroidal involvement in both ocular and non-ocular Behçet disease patients that show any kind of vascular pathology. In contrast, our study did not find any difference with the healthy group as regard to CC flow area. We believe that OCTA may be helpful in the follow-up of BU patients but we were unable to fully support our theory due to the limited sample size of our study.

Investigating flow characteristics around the ONH could provide insight into the pathogenesis of uveitis. To best of our knowledge, only one study by Emre et al.[34] showed such changes on OCTA images of the ONH in 5 (19.2%) eyes with non-perfusion/hypo-perfusion areas and in 1 (3.8%) eye with telangiectatic capillary collaterals. However, they did provide any detail on the ONH flow and non-flow area, or CVD at the OD-centered images. Wang et al.[40] compared the perfusion of the optic nerve in 36 MS patients and 27 healthy controls using OCTA and showed a lower ONH flow index (defined as the average flow signal within the ONH) in patients with optic neuritis associated with MS compared to the control group. They stated this reduction could be due to the generally decreased regional metabolic activity following nerve fiber loss, which results in decreased blood flow secondary to auto-regulatory mechanisms. We believe that there might be hemodynamic impairments in the ONH with similar mechanisms in Behçet disease. In support of these findings, we found a significantly decreased ONH flow area and CVD at the OD-centered 4.5 x 4.5 mm^2 area but increased ONH non-flow area compared to the control group, although only 5 (12.5%) eyes had visible optic disc pallor on fundus examination. We believe this finding may help to explain the reason of the low visual acuity in eyes without any significant optic nerve head changes on fundus examination. Additionally, optic neuropathy as neurologic involvement in Behçet's disease has been reported as ischemic optic atrophy, retrobulbar neuritis and anterior/posterior ischemic optic neuropathy and it can also be associated with optic disc edema.[41,42] Based on this, the optic disc pallor detected in 5 eyes (12.5%) in this study might be the sequel of previous optic neuropathy.

Khairallah et al.[11] demonstrated that BCVA (logMAR) was negatively correlated with CVD in SCP and DCP. On the other hand, BCVA (logMAR) was positively correlated with the FAZ area for the SCP and DCP, the presence of perifoveal capillary arcade disruption and capillary abnormalities in the SCP, and capillary network disorganization in SCP and DCP in BU patients.[11] We found that the BCVA (logMAR) showed a negative correlation with the ONH flow area, CVD in the OD-centered area, SCP flow area and parafoveal SCP thickness in BU patients. The reason could be the reduced blood flow (smaller vessel area) leading to dysfunctional retinal ganglion cells and lower visual acuity.

To the best of our knowledge, this is the first detailed report on ONH parameters with OCTA in BU patients. The limitations of our study include the limited number of patients, the inability to evaluate the changes in the patients during the attacks (activity and remission periods), and the fact that the treatment options could have modified the results. Other limitations, as reported in the literature,[43,44] are the fact that the device can only measure a specific area with a small field of view (6 x 6 mm macular or 4.5 x 4.5 mm^2 ONH), device-related segmentation errors, ghost images due to RPE reflections and the inability of the device to detect low flow. We were also unable to correlate OCTA findings with FA in the present study.

In conclusion, OCTA might provide valuable information on Behçet uveitis and lead to a better understanding of structural changes in the retina, choroid and ONH. In the present study, we found decreased ONH flow area and CVD in the OD-centered area together with increased ONH non-flow area in Behçet patients. The BCVA (logMAR) showed a negative correlation with the ONH flow area, CVD in the OD-centered area, SCP flow area and parafoveal SCP thickness. To ability to measure the CVD, and non-flow and flow areas of the ONH by OCTA could show the normally unobservable effects of Behçet disease. In the light of the data from the current study and other studies in the literature, we believe that Behçet uveitis patients with low visual acuity could have micro-vascular changes of the optic nerve head in addition to retinal vascular involvement during the disease course, independent of its duration, and that these could contribute to the decreased visual acuity. The authors believe that research on the retinal vascular plexus and the micro-vascular structure of the ONH might provide new insights into the pathology of Behçet uveitis. Further studies with a larger number of patients are required for better understanding of this recent diagnostic technique.

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